REMARKS

Claims 1, 4, 5, 7 – 21, 23 and 24, as amended, are pending in the application. Claims 2, 3, 6, and 22 are canceled without prejudice. The amendments to claims 1 and 14 were submitted to add a specific time range for administering the ospemifene in conjunction with eating. This range was set forth in now-canceled claim 2. Therefore, no new matter is added.

Reconsideration and re-examination of this application in view of the following remarks is hereby respectfully requested.

I. REJECTION UNDER 35 U.S.C. 112, SECOND PARAGRAPH

Claims 1, 7, 10 – 11 and 21 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner objects to the phrase "…said foodstuff being taken shortly before…shortly after" as not providing a standard for ascertaining the requisite degree. Without acquiescing to the rejection, applicant points out that the amendment to claims 1 and 14 adds a specific range of time to the claim. Therefore, the claims are clearly definite and applicant respectfully requests that the rejection be reconsidered and withdrawn.

II. FIRST REJECTION UNDER 35 U.S.C. §103(a)

Claims 1, 3 – 5 , 7, 10 – 11, 14 and 18 – 20 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over DeGregorio et al. (US 5,750,576) in view of Anttila (1997) and further in view of Guidance for Industry (2002).

The Examiner argues that DeGregorio et al. teach the treatment of osteoporosis by administering ospemifene orally in dosage amounts of 5-100 mg/day. The Examiner admits that DeGregorio does not teach the administration of the drug in connection with the intake of food, much less within a certain time period of eating. The Examiner cites Antilla to show that "structurally similar compounds" (i.e. toremifene) are known in the art to be administered with or without food. The Examiner erroneously argues that "all food has nutritional value and therefore would cause the secretion of bile acids" and therefore would "enhance the bioavailability of toremifene." The Examiner also

mentions that 60 mg of toremifene is administered. The Guidance for Industry is alleged to teach that studies to determine the effect of food intake on bioavailability are routinely performed as part of the drug development process and that food effects are generally greatest when the drug product is administered shortly after a meal is ingested.

In light of the combination of these three references the Examiner concludes that it would have been obvious to expand the teachings of DeGregorio et al. to include the teachings of Antilla and administer ospemifene at a dosage of 60 mg/day for the treatment of osteoporosis with a reasonable expectation of success. According to the Examiner, because Antilla teaches that toremifene can be administered with or without food and DeGregorio is silent regarding food intake with ospemifene, one would be motivated to administer ospemifene "with or without food with the expectation of success that the effect will be the same when ospemifene is administered with or without food." Allegedly, one is further motivated because of the teachings of Guidance for Industry teaches that drugs should be tested under both fed and fasting conditions to help determine the precise administration instructions. Therefore, the Examiner concludes "the combination of the cited prior art would have been prima facie obvious at the time the claimed invention was filed." Applicants respectfully traverse.

Applicant has mentioned the deficiencies of DeGregorio et al. and Anttila on several occasions previously and references those arguments here. The Examiner admits that DeGregorio et al. is silent regarding the administration of food. The Examiner also admits that Anttila teaches the administration of a different drug (toremifene) with food. The Examiner continues to erroneously argue that administering toremifene with food inherently enhances the bioavailability of the toremifene, but hedges that argument by stating the measure of success is merely that a drug (whether toremifene or ospemifene) can be administered *equally* with or without food. The Examiner also concludes that the combination of references establishes a prima facie case of obviousness alleging that is the end of the analysis.

Applicant points out that the method is directed to *enhancing the bioavailability of ospemifene.* The Examiner's reasons for rejecting the claims on the basis of obviousness are deficient for a number of reasons but applicant stresses this point. It is

improper in this context to simply hold that the measure of success is that administering ospemifene with food would not impair the bioavailability.

Furthermore, Applicant has already submitted a Declaration establishing, among other things, that Anttila does *not* show that the bioavailability of toremifene is improved when administered with food (Lammintausta Declaration ¶23). The Declaration also establishes that even though ospemifene and toremifene are structural relatives, their pharmacokinetics are significantly different in regard to their elimination rates and metabolism (Lammintausta Declaration ¶22). The Declaration also confirms that applicant unexpectedly found a significant 2-3 fold improvement of ospemifene bioavailability when administered with food. This unexpected finding of significant 2-3 fold improvement of ospemifene bioavailability with food has very significant practical consequences. For example, in a large clinical study, ospemifene administered in 60 mg daily doses given with food shows significant benefit in treating dyspareunia. Since the FDA and other regulatory agencies are requiring the use of the lowest effective doses of drugs for these sorts of non-fatal disorders, it is critical that the patient be advise to take ospemifene with food. If administered without food the effective dose to be advised in the product label should be between 120-180 mg daily instead. This is not the case with other SERMs currently in clinical use (Lammintausta Declaration ¶28).

Because DeGregorio et al. in view of Anttila and further in view of Guidance for Industry (2002) do not teach or suggest a method to enhance the bioavailability of orally-administered ospemifene, much a less a significant 2-3 fold improvement as demonstrated by Applicant, they do not render obvious the claimed invention. Therefore, Applicant respectfully requests that this obviousness rejection be reconsidered and withdrawn.

III. SECOND REJECTION UNDER 35 U.S.C. §103(a)

Claims 1, 8-9, 12-13, 15-17 and 21-24 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Halonen et al. (US 6,245,819) in view of Anttila (1997) and further in view of Guidance for Industry (2002).

The Examiner argues that Halonen et al. teaches administering ospemifene, SERM, to women suffering from vaginal dryness. The Examiner acknowledges that

Halonen et al. fail to teach the administration of ospemifene with food. The Examiner relies upon Antilla for the same reasons as the first obviousness rejection, i.e. to show that "structurally similar compounds are known in the art to be administered with or without food." Similarly, Guidance for Industry is cited for the same reasons as above to demonstrate that food bioavailability studies are conducted to compare the effects of drugs in patients in fed versus fasted states.

The Examiner alleges that Halonen et al. do not specifically teach treating urogenital atrophy but that they do mention that during and after menopause elderly women develop symptoms which are due to estrogen deficiency such as vaginal dryness and urinary incontinence. The Examiner then states that "based on [this] teaching alone one of ordinary skill in the art would have been motivated to inhibit vaginal atrophy and urogenital atrophy with ospemifene because these diseases are estrogen related disorders and reasonable (sic.) to be treated with an estrogen receptor modulator." The Examiner further alleges that the varying point of administration of ospemifene (such as 2 hours, one hour, 0.5 hour) after starting food intake is mere optimization. Applicant disagrees and respectfully traverses.

In this rejection, the only reference that is different from the first obviousness rejection discussed above is Halonen et al. As admitted by the Examiner, Halonen et al. does not teach or suggest the administration of ospemifene with food. Neither Halonen et al. nor the secondary references, Anttila and Guidance for Industry, teach or suggest that the bioavailability of an orally administered SERM, much less ospemifene, would be enhanced by food intake. Despite the fact that enhancing the bioavailability of ospemifene is a necessary limitation in the claims, the Examiner hedges the rejection by stating the measure of success is merely that a drug (whether toremifene or ospemifene) can be administered *equally* with or without food. By doing this, the Examiner ignores a critical element in the claim and fails to make a *prima facie* case of obviousness. Even if the Examiner had made a *prima facie* case, the Examiner continues to ignore several facts established by the Lammintausta Declaration that would rebut any such finding. These facts include the unexpected and significant improvement in bioavailability, the unpredictability of SERMs in general and the specific pharmacokinetic differences between toremifene and ospemifene, among others.

A finding of obviousness requires that the prior art both suggest the invention and provide one of ordinary skill with a reasonable expectation of success. *In re O'Farrell* 853 F.2d 894, 903, 7 USPQ2d 1673 (Fed. Cir.1988). Secondary considerations such as unexpected results must be considered if present. *Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 1538-39, 218 USPQ 871, 879 (Fed. Cir. 1983); *In re Merck & Co., Inc.,* 800 F.2d 1091, 1096, 231 USPQ 375, 378 (Fed. Cir. 1986). The USPTO must consider rebuttal evidence of teaching away. *See In re Sullivan,* 84 USPQ2d 1034, 1038 (Fed. Cir. 2007) (The Federal Circuit remanded an appeal back to the BPAI for failure to consider rebuttal evidence put forth by the Applicant during prosecution).

Because the rejection fails to address, among other things, at least one critical element in the claims and the evidence of unexpected and significant improvement in bioavailability, it is deficient in teaching or suggesting the claimed invention. Applicant respectfully requests that the obviousness rejection in light of Halonen et al. in view of Anttila and further in view of Guidance for Industry be reconsidered and withdrawn.

IV. FIRST REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1, 3-5 and 7-24 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,984,665 ("the '665 patent") in view of Guidance for Industry (2002). The Examiner submits that "the '665 patent differs from the claimed invention insofar as it fails to expressly claim a method of enhancing bioavailability." The Examiner cites Guidance for Industry to show that food effect bioavailability studies are conducted with new drugs to compare fed and fasted conditions. Applicant submits that this combination of references is deficient in teaching or suggesting the claimed invention in for the same reasons that the combination of Halonen et al., Antilla and Guidance for Industry is deficient. The rejection omits at least one critical limitation in the claims and ignores the Declaration evidence. Therefore, Applicant respectfully requests that the obviousness-type double patenting rejection of claims 1, 3-5 and 7-24 over the '665 patent in view of Guidance for Industry be withdrawn.

V. SECOND REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Claims 1, 3-5 and 7-24 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,245,819 ("Halonen et al.") in view of Guidance for Industry.

The Examiner submits that "[Halonen et al.] differs from the claimed invention insofar as it fails to expressly claim a method of enhancing bioavailability." The Examiner cites Guidance for Industry to show that food effect bioavailability studies are conducted with new drugs to compare fed and fasted conditions. Applicant submits that this combination of references is deficient in teaching or suggesting the claimed invention in for the same reasons that the combination of Halonen et al., Antilla and Guidance for Industry is deficient. The rejection omits at least one critical limitation in the claims and ignores the Declaration evidence. Therefore, Applicant respectfully requests that the obviousness-type double patenting rejection of claims 1, 3-5 and 7-24 over Halonen et al. in view of Guidance for Industry be withdrawn.

VI. THIRD REJECTION FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

Applicant notes that there is a third obviousness-type double patenting listed in the rejection but it appears to be identical to the first in that the claims are rejected as being unpatentable over claims 1-3 of U.S. Patent No. 6,984,665 ("the '665 patent") in view of Guidance for Industry (2002) for substantially the same reasons above. Applicant refers to the arguments made above in reply to the First Rejection for Obviousness-Type Double Patenting and respectfully requests that the obviousness-type double patenting rejection of claims 1, 3-5 and 7-24 over the '665 patent in view of Guidance for Industry be withdrawn.

VII. ADDRESSING COMMENTS MADE REGARDING LAMMINTAUSTA DECLARATION

Applicant notes that at the end of the office action the Examiner selectively addresses points made in the Lammintausta Declaration. Specifically, the Examiner argues that it is immaterial whether SERMs are unpredictable regarding their estrogenicity in particular tissues. Applicant respectfully disagrees. The Examiner relies on structural similarity and class membership to argue that one of ordinary skill

would substitute one SERM (ospemifene) for another (e.g. toremifene) to support her combination of references. It is improper for the Examiner to argue that one would be motivated to substitute ospemifene for other SERMs based solely on structure while ignoring known differences in pharmacology and pharmacokinetics that would teach away from a particular combination of references.

Applicant also notes that the Examiner does not address other evidence provided in the Declaration including the unexpected and significant increase in bioavailability demonstrated by utilizing the claimed invention. As stated above, secondary considerations must be considered by the USPTO when considering questions of obviousness.

In view of the above amendments and remarks, it is submitted that the claims are in condition for immediate allowance. A prompt notice to that effect is earnestly solicited.

Respectfully submitted,

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